IMMUNOLOGICAL CONTROL OF β-AMYLOID LEVELS *IN VIVO*

Abstract of the Disclosure

The present invention provides an antibody which catalyzes hydrolysis of β-amyloid at a predetermined amide linkage. The antibody preferentially binds a transition state analog which mimics the transition state adopted by β-amyloid during hydrolysis at a predetermined amide linkage and also binds to natural β-amyloid with sufficient affinity to detect by ELISA. Alternatively, the antibody preferentially binds a transition state analog which mimics the transition state adopted by β-amyloid during hydrolysis at a predetermined amide linkage, and does not bind natural β-amyloid with sufficient affinity to detect by ELISA. Antibodies generated are characterized by the amide linkage which they hydrolyze. Specific antibodies provided include those which catalyze the hydrolysis at the amyloid linkages between residues 39 and 40, 40 and 41, and 41 and 42, of β-amyloid. The present invention also provides a vectorized antibody which is characterized by the ability to cross the blood brain barrier and is also characterized by the ability to catalyze the hydrolysis of β-amyloid at a predetermined amide linkage. The vectorized antibody can take the form of a bispecific antibody, which has a first specificity for the transferrin receptor and a second specificity for a transition state adopted by β-amyloid during hydrolysis. The present invention also provides a method for sequestering free β-amyloid in the bloodstream of an animal by intravenously administering antibodies specific for β-amyloid to the animal in an amount sufficient to increase retention of β-amyloid in the circulation. In addition, the present invention provides a method for sequestering free β-amyloid in the bloodstream of an animal by immunizing an

animal with an antigen comprised of an epitope which is present on β-amyloid endogenous to the animal under conditions appropriate for the generation of antibodies which bind endogenous β-amyloid. Therapeutic applications of these methods include treating patients diagnosed with, or at risk for Alzheimer's disease. Methods for reducing levels of β-amyloid in the brain of an animal, by intravenously administering antibodies specific for endogenous β-amyloid to the animal, or by immunizing the animal with an antigen comprised of an epitope which is present on endogenous β-amyloid are also provided. In one embodiment, the antigen used to generate the antibodies is a transition state analog which mimics the transition state adopted by β-amyloid during hydrolysis at a predetermined amide linkage. Similar methods which utilize or generate antibodies which catalyze the hydrolysis of β-amyloid for reducing levels of circulating β-amyloid in an animal, and also for preventing the formation of amyloid plaques in the brain of an animal, and also for disaggregating amyloid plaques present in the brain of an animal, are also provided. Also provided is a method for generating antibodies which catalyze hydrolysis of a protein or polypeptide by immunizing an animal with an antigen comprised of an epitope which has a statine analog which mimics the conformation of a predetermined hydrolysis transition state of the polypeptide. A similar method, which utilizes reduced peptide bond analogs to mimic the conformation of a hydrolysis transition state of a polypeptide, is also provided.